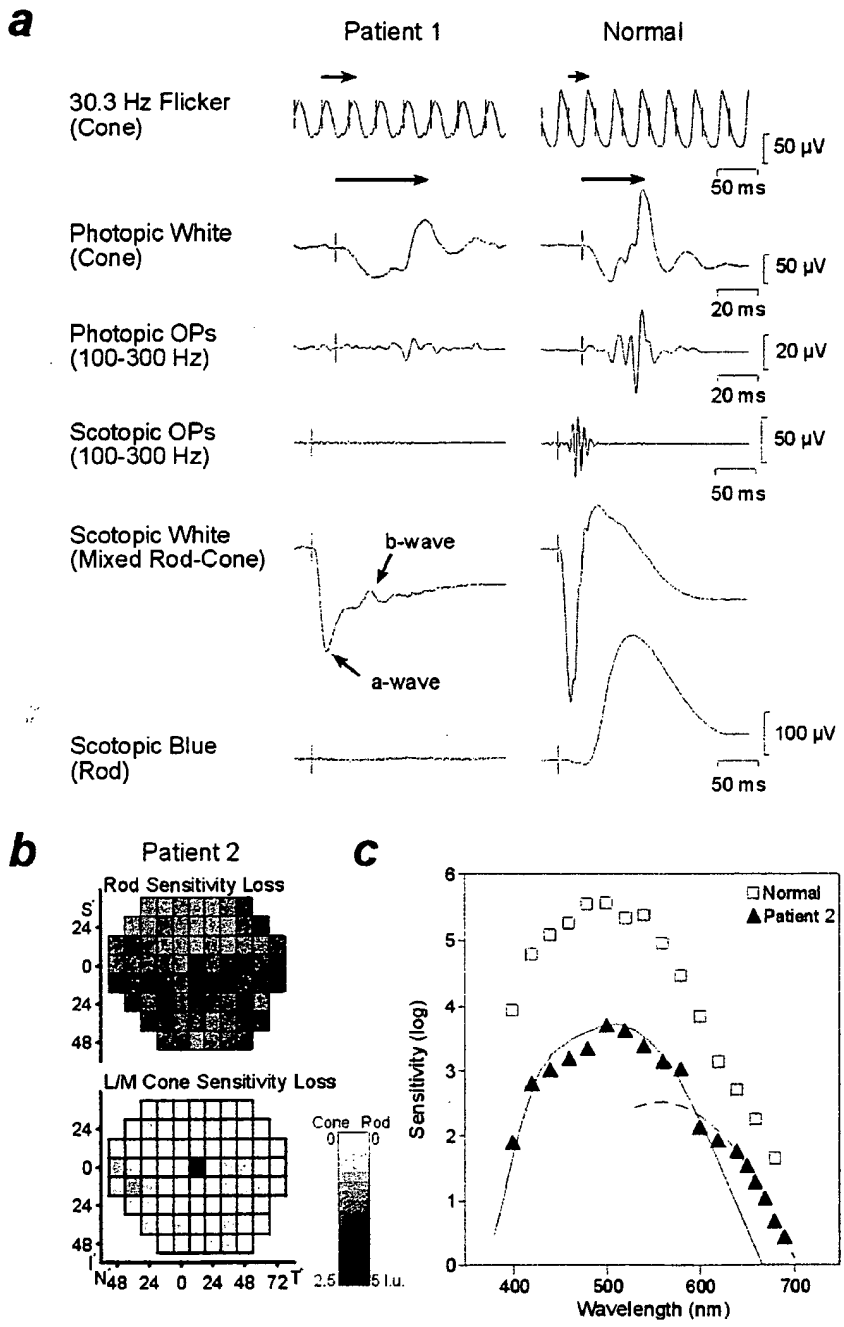

a
Patient 1
Normal
30.3 Hz Flicker (Cone)
50 µV
50 ms
Photopic White (Cone)
50 µV
20 ms
Photopic OPs (100-300 Hz)
20 µV
20 ms
Scotopic OPs (100-300 Hz)
50 µV
50 ms
Scotopic White (Mixed Rod-Cone)
b-wave
a-wave
Scotopic Blue (Rod)
100 µV
50 ms
b
Patient 2
Rod Sensitivity Loss
L/M Cone Sensitivity Loss
Cone Rod
2.5 5 l.u.
c
Normal
Patient 2
Sensitivity (log)
Wavelength (nm)

FIGURE 1

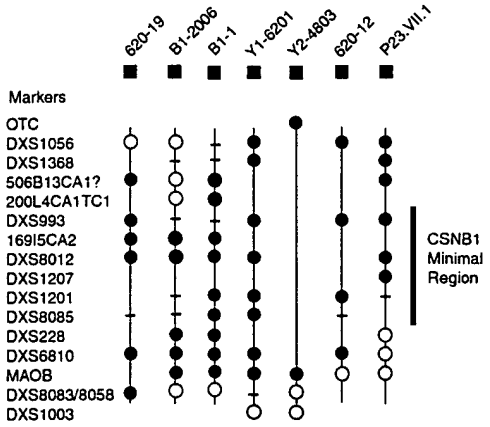
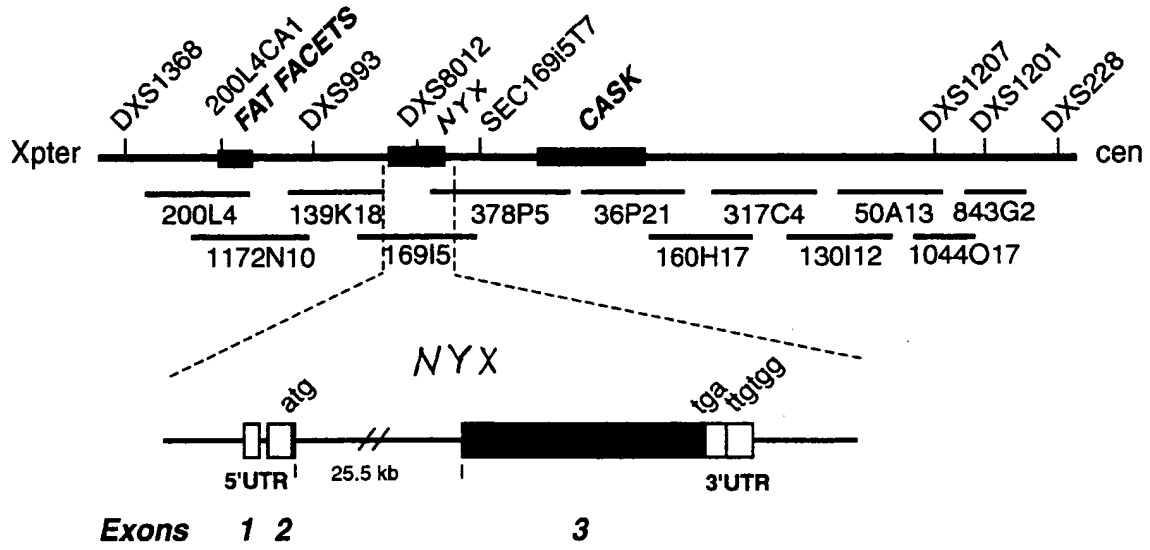

620-19
B1-2006
B1-1
Y1-6201
Y2-4603
620-12
P23.VII.1
Markers
OTC
DXS1056
DXS1368
506B13CA1?
200L4CA1TC1
DXS993
169I5CA2
DXS8012
DXS1207
DXS1201
DXS8085
DXS228
DXS6810
MAOB
DXS8083/8058
DXS1003
CSNB1
Minimal
Region

FIGURE 2

a Physical map of the CSNB1 minimal region and genomic organization of *NYX*



b Leucine-rich repeats and the distribution of mutations in the Nyctalopin protein

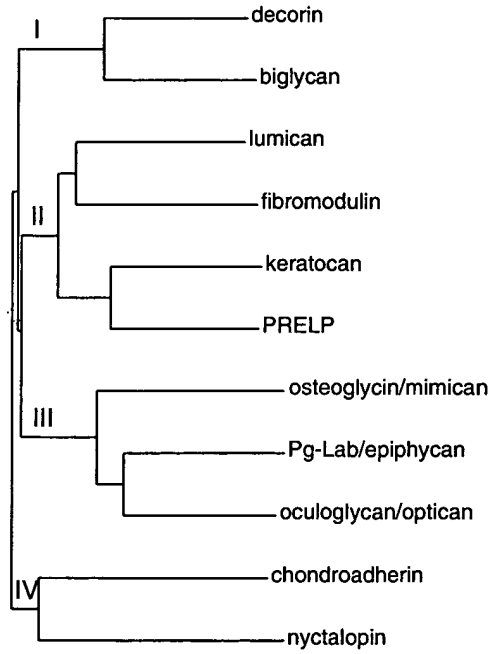
```
MKGRGMLVLLLHAVVLGLPSAWAVGA ARA PAA A STVERG SVR DR   - 50
                           del
1.   AGLLRVPAELPCEAVSIDLDRNGL                          - 74
2.   RFLGERAFGTLPSLRRLSLRHNNL                          - 98
3.   SFITPGAFKGLPRLAELRLAHNGDL                         - 123
4.   RYLHARTFAALSRLRRLDLAACRL                          - 147
5.   FSVPERLLAELPALRELAAFDNLFRRVPGALRGL                - 181
6.   ANLTHAHL15LRRLRSLSLQANRV                          - 218
      ERGRIEAVASSSLQG
7.   RAVHAGAFGDCGVLEHLLLNDNLL                          - 242
8.   AELPADAFRGLRRLRTLNLGGNAL                          - 266
9.   DRVARAWFADLAELELLYLDRNSI                          - 290
10.  AFVEEGAFQNLSGLLALHLNGNRL                          - 314
11.  TVLAWVAFQPGFFLGRLFLFRNPW                          - 338
        β-sheet     α-helix
                    |
  DCRLEWLRDWMEGSGRVTDVP ASPGSVAGLDLSQVTFGRSSDGL VD   - 388
PEELNLTTSSPGPSPEPAATTVSRFSSLLSKLLAPRVPVEEAANTTGGLA   - 438
NASLSDSLSSRGVGGAGRQPWFLLASCLLPSVAQHVVFGLQMD         - 481
```

^ *insertions of SVPERLL, GLR and RLR, respectively*
v *most likely signal peptide cleavage site*

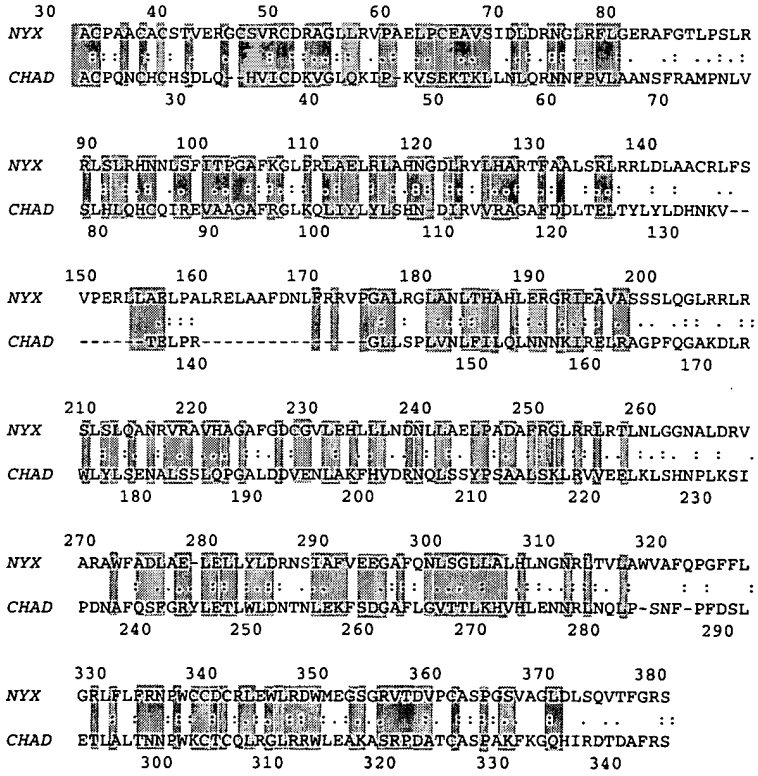
FIGURE 3

FIGURE 3
CONT.

C



D



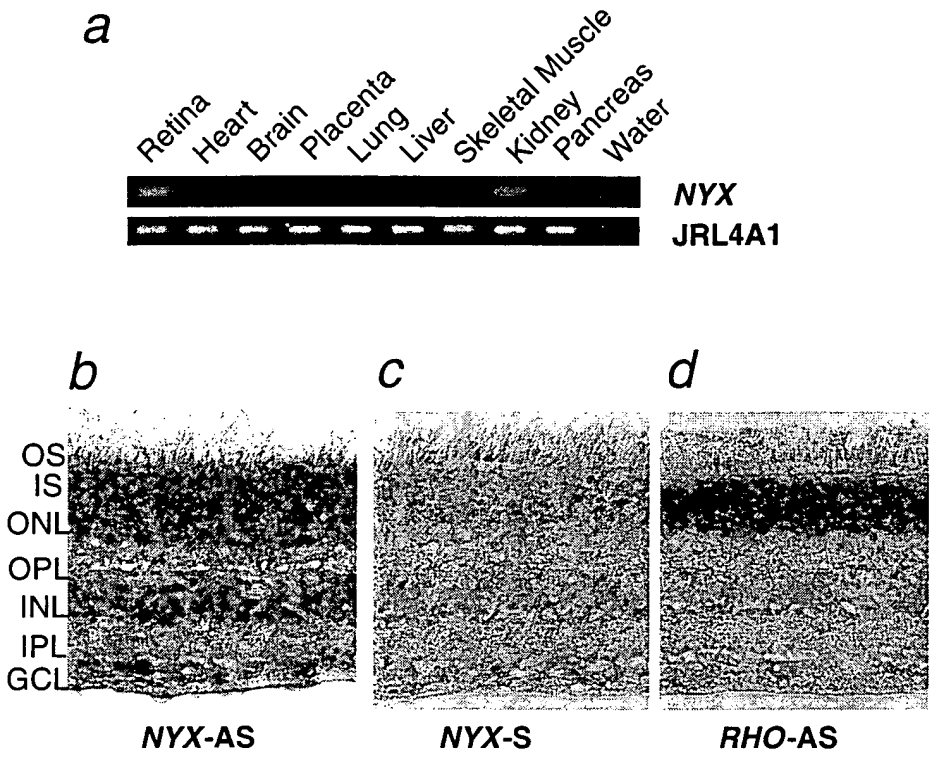

a
Retina
Heart
Brain
Placenta
Lung
Liver
Skeletal Muscle
Kidney
Pancreas
Water
NYX
JRL4A1
b
c
d
OS
IS
ONL
OPL
INL
IPL
GCL
NYX-AS
NYX-S
RHO-AS

FIGURE 4

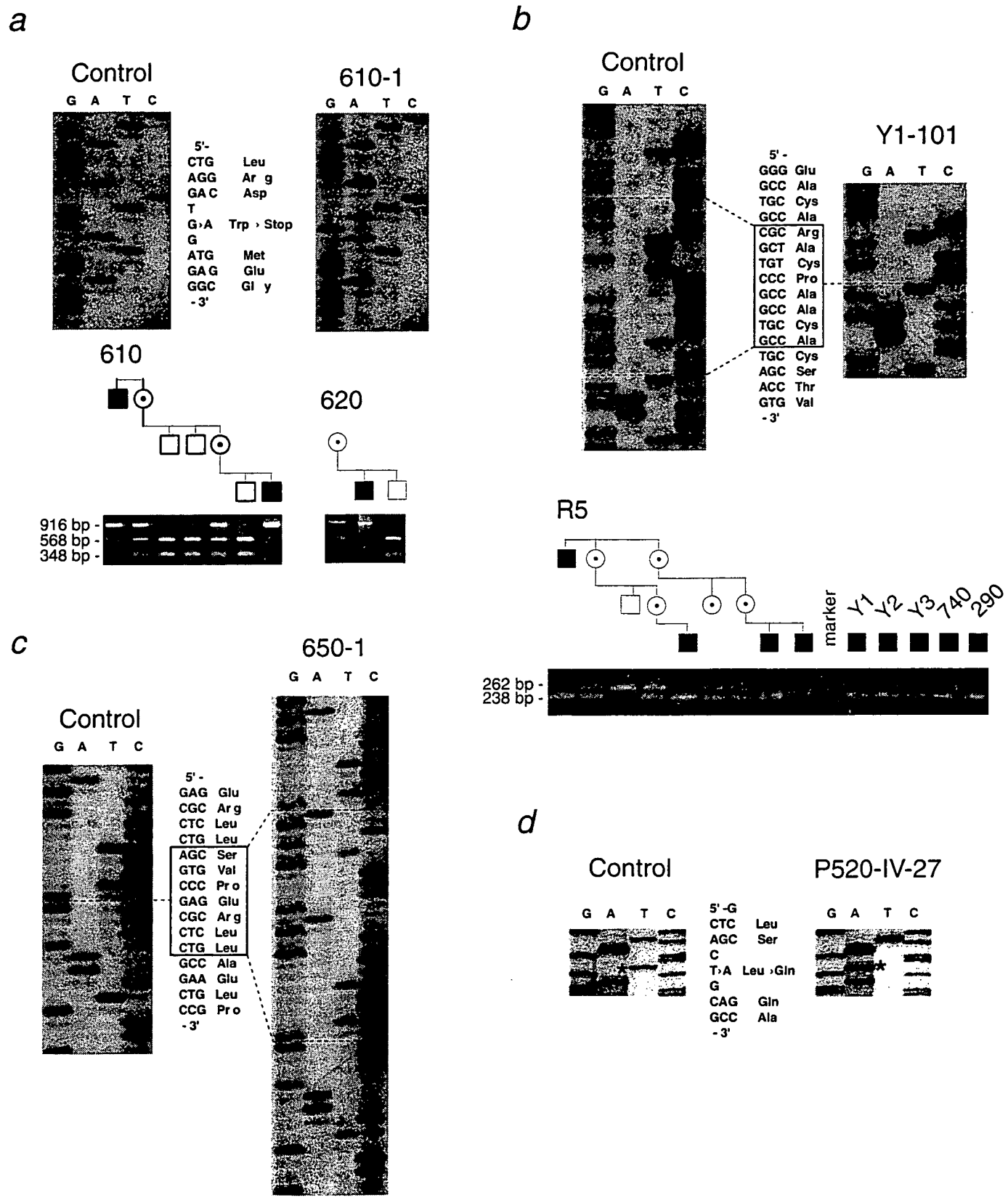

a
Control
G A T C
610-1
G A T C
5'-
CTG Leu
AGG Ar g
GA C Asp
T
G›A Trp › Stop
G
ATG Met
GA G Glu
GGC Gl y
-3'
610
620
916 bp -
568 bp -
348 bp -
b
Control
G A T C
Y1-101
G A T C
5'-
GGG Glu
GCC Ala
TGC Cys
GCC Ala
CGC Arg
GCT Ala
TGT Cys
CCC Pro
GCC Ala
GCC Ala
TGC Cys
GCC Ala
TGC Cys
AGC Ser
ACC Thr
GTG Val
-3'
R5
marker
Y1
Y2
Y3
740
290
262 bp -
238 bp -
c
650-1
G A T C
Control
G A T C
5'-
GAG Glu
CGC Ar g
CTC Leu
CTG Leu
AGC Ser
GTG Val
CCC Pr o
GAG Glu
CGC Ar g
CTC Leu
CTG Leu
GCC Ala
GAA Glu
CTG Leu
CCG Pr o
-3'
d
Control
P520-IV-27
G A T C
G A T C
5'-G
CTC Leu
AGC Ser
C
T›A Leu ›Gln
G
CAG Gln
GCC Ala
-3'

FIGURE 5

Table 1 • Nyctalopin mutations in families with complete CSNB

Family[a]	Origin	Mutation[b]	Codon change	Predicted effect on nyctalopin
290,740,830,Y1,Y2,Y3,R5[c]	USA	85-108del24nt[d]	RACPAACA29-36del	partial loss of N-terminal cysteine cluster
P23.340 (2) (ref 13)	Netherlands	452C>T	P151L	missense, proline to leucine
650 (2)	Canada	464^465ins21nt	SVPERLL155-156ins	expansion of LRR5[e]
750[f] (1),780 (1)	Canada,USA	551T>C	L184P	missense, leucine to proline
540 (6)(ref 28, family 2)	Germany	556-618del50ins3nt		frameshift with stop at codon 259
640 (2)	USA	619^620ins9nt	LLR207-208ins	expansion of LRR6
R7 (7)	USA	628^629ins9nt	CLR209-210ins	expansion of LRR6
P520 (2)	Netherlands	638T>A	L213Q	missense, leucine to glutamine
580 (2)	Canada	647A>G	N216S	missense, asparagine to serine
550 (9)(ref 28, family 3)	Germany	695T>C	L232P	missense, leucine to proline
B1 (3)	USA	792C>G	N264K	missense, asparagine to lysine
B660 (1)	USA	854T>C	L285P	missense, leucine to proline
B2 (5)	USA	893T>C	F298S	missense, phenylalanine to serine
610, 620 (4,10)	Costa Rica	1049G>A	W350X	protein truncation, loss of GPI-anchoring

[a] families Y1, Y2, Y3, R5, R7, B1 and B2 were first reported in reference 25. Earlier reports on other families is indicated following the family designation.
[b]following the recommendations of Nomenclature Working Group.
[c]number of affected males in these families: 8, 1, 4, 8, 2 and 5, respectively. For all other families in this table this information is shown in first set of parentheses following the family designation.
[d]in the analysis of X chromosomes with this deletion, we observed identical haplotypes across Xp11.4 from *DXS556* to *DXS228* with some chromosomes diverging proximally or distally beyond this region (15 markers tested)
[e]LRR, leucine-rich repeat.
[f]Patient 1, whose electrophysiological results are shown in Fig. 1.

FIGURE 6

```
         -98                                                                                    -1
         Ggctgaggga gtggaggggg acctcagagg agcaggacca gggagactcc caggacggta ggggtcccac ggctgggtgg tcctaagcca ctgggtgg
```

```
     -98                                                                                        -1
         Ggctgagggagtggagggggacctcagaggagcaggaccagggagactcccaggacggtaggggtcccacggctgggtggtcctaagccactgggtgg

     1/1 ATGaaaggccgagggatgttggtcctgcttctgcatgcggtggtcctcggcctgcccagcgcctgggccgtgggggcctgcgcccgcgcttgtcccgccgcctgcgcctgcagcaccgtg
         M  K  G  R  G  M  L  V  L  L  L  H  A  V  V  L  G  L  P  S  A  W  A  V  G  A  C  A  R  A  C  P  A  A  C  A  C  S  T  V

  121/41 gagcgcggctgctcggtgcgctgcgaccgcgcgggcctcctgcgggtgccggccgagctcccgtgcgaggcggtctccatcgacctggaccggaacggcctgcgcttcctgggcgagcga
         E  R  G  C  S  V  R  C  D  R  A  G  L  L  R  V  P  A  E  L  P  C  E  A  V  S  I  D  L  D  R  N  G  L  R  F  L  G  E  R

  241/81 gccttcggcacgctgccgtccttgcgccgcctgtcgctgcgccacaacaacctgtccttcatcacgcccggcgccttcaagggcctgccgcgcctggctgagctgcgcctggcgcacaac
         A  F  G  T  L  P  S  L  R  R  L  S  L  R  H  N  N  L  S  F  I  T  P  G  A  F  K  G  L  P  R  L  A  E  L  R  L  A  H  N

 361/121 ggcgacctgcgctacctgcacgcgcgcaccttcgcggcgctcagccgcctgcgccgcctagacctagcagcctgccgcctcttcagcgtgcccgagcgcctcctggccgaactgccggcc
         G  D  L  R  Y  L  H  A  R  T  F  A  A  L  S  R  L  R  R  L  D  L  A  A  C  R  L  F  S  V  P  E  R  L  L  A  E  L  P  A

 481/161 ctgcgcgaactcgccgccttcgacaacctgttccgccgcgtgccgggcgcgctgcgcggcctggccaacctgacgcacgcgcacctggagcgcggccgcatcgaggcggtggcctccagc
         L  R  E  L  A  A  F  D  N  L  F  R  R  V  P  G  A  L  R  G  L  A  N  L  T  H  A  H  L  E  R  G  R  I  E  A  V  A  S  S

 601/201 tcgctgcagggcctgcgccgcctgcgctcgctcagcctgcaggccaaccgcgtccgtgccgtgcacgctggcgccttcggggactgtggcgtcctggagcatctgctgctcaacgacaac
         S  L  Q  G  L  R  R  L  R  S  L  S  L  Q  A  N  R  V  R  A  V  H  A  G  A  F  G  D  C  G  V  L  E  H  L  L  L  N  D  N

 721/241 ctgctggccgagctcccggccgacgccttccgcggcctgcggcgcctgcgcacgctcaacctgggtggcaacgcgctggaccgcgtggcgcgcgcctggttcgctgacctggccgagctc
         L  L  A  E  L  P  A  D  A  F  R  G  L  R  R  L  R  T  L  N  L  G  G  N  A  L  D  R  V  A  R  A  W  F  A  D  L  A  E  L

 841/281 gagctgctctacctggaccgcaacagcatcgccttcgtggaggagggcgccttccagaacctctcgggtctcctcgcgctgcacctcaacggcaaccgcctcaccgtgctcgcctgggtc
         E  L  L  Y  L  D  R  N  S  I  A  F  V  E  E  G  A  F  Q  N  L  S  G  L  L  A  L  H  L  N  G  N  R  L  T  V  L  A  W  V

 961/321 gccttccagcccggcttcttcctgggccgcctcttcctcttccgcaacccgtggtgctgcgactgccgtctggagtggctgagggactggatggagggctccggacgtgtcaccgacgtg
         A  F  Q  P  G  F  F  L  G  R  L  F  L  F  R  N  P  W  C  C  D  C  R  L  E  W  L  R  D  W  M  E  G  S  G  R  V  T  D  V

1081/361 ccgtgcgcctccccgggctccgtggccggcctggacctcagccaggtgaccttcgggcgctcctccgatggcctctgtgtggaccccgaggagctgaacctcaccacgtccagtccaggc
         P  C  A  S  P  G  S  V  A  G  L  D  L  S  Q  V  T  F  G  R  S  S  D  G  L  C  V  D  P  E  E  L  N  L  T  T  S  S  P  G

1201/401 ccgtccccagaaccagcggccaccaccgtgagcaggttcagcagcctcctctccaagctgctggccccgagggtcccggtggaggaggcggccaacaccactgggggctggccaacgcc
         P  S  P  E  P  A  A  T  T  V  S  R  F  S  S  L  L  S  K  L  L  A  P  R  V  P  V  E  E  A  A  N  T  T  G  G  L  A  N  A

1321/441 tccctgtccgacagcctctcctcccgtggggtgggaggcgcgggccggcagccctggtttctcctcgcctcttgtctcctgcccagcgtggcccagcacgtggtgtttggcctgcagatg
         S  L  S  D  S  L  S  S  R  G  V  G  G  A  G  R  Q  P  W  F  L  L  A  S  C  L  L  P  S  V  A  Q  H  V  V  F  G  L  Q  M

1441/481 gactgacctggccagagggggggaaagtttgcttaactgggcttgagtgtgtttgtggtaaggggagaggagccggaatggagggcagaggtgaaaatcccagtggagggtggaaggaacc
         D  *

    1561 Gtttgcctccagagatggccccagggagaacacagggacgtgccactcgaggggggaggatggtatggatttctgcttttgtcacacgggcatccattggaaaagagaagcaagaatgaac
    1681 gtgggccctcgggtgggaagactaggaatcggaagcttctagggcttcacatcccttcccctcccctccccttcccctcatcttccaggcaacagtgcctgcaaggcctgaattagagag
    1801 acttccattggctaagtagttaagagccgtcccatttctcctggcggggtaacccattacaccgaagtcctttgttttctaccacaatcctcctcctcctctccaggggcctggaaacac
    1921 taggattcaggaaggtaggcaggacgtgagagaagggagatgggagagagatttaagacaaagggtggcggtggttcctggggtctgagatgtgttaggaggcgtttaaaacaaagatcc
    2041 agttcatttactccacagttattcccagggctggccctagccacaaaggaactttagggcagggtagggaaaaaggggcagcaggggggtgtgtttgtggacaaataaatttgtaaagtc
    2161 cgaggattaaaaaaaaaaaaaggttaaaccggtttctctactgctggacttttcagagtctttc
```

FIGURE 7